**Annals of Clinical and Analytical Medicine**
*Original Research*

# Can NLR/PLR/CEA be a marker for predicting a complete pathological response in locally advanced rectal cancer?

Prognostic markers on complete pathological response in rectal cancer

Hüseyin Çiyiltepe[1], Ebubekir Gündeş[2], Durmuş Ali Çetin[3], Ulaş Aday[4], Emre Bozdağ[5], Selçuk Gülmez[6], Orhan Uzun[6], Aziz Serkan Senger[6], Erdal Polat[6], Mustafa Duman[6]
[1]Department of Gastroenterological Surgery, University of Health Sciences, Istanbul Fatih Sultan Mehmet Training and Research Hospital, Istanbul
[2]Department of Gastroenterological Surgery, University of Health Sciences, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır
[3]Department of Gastroenterological Surgery, University of Health Sciences, Tepecik Training and Research Hospital, İzmir
[4]Department of General Surgery, University of Dicle, Diyarbakır
[5] Department of Gastroenterological Surgery, University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, İstanbul
[6] Department of Gastroenterological Surgery, University of Health Sciences, Istanbul Kartal Koşuyolu High Speciality Training and Research Hospital, Istanbul, Turkey

**Abstract**

Aim: The standard treatment for locally advanced (T3-4 and/or N +) rectal cancer (LARC) is Total Mesorectal Excision (TME) and adjuvant chemotherapy after neoadjuvant chemo-radiotherapy (n-CRT). Various clinical or pathological complete response (pCR) rates after neoadjuvant therapy have been reported in the literature. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) or carcinoembryonic antigen (CEA) levels are used as prognostic markers for many tumors.The aim of this study is to investigate the relationship between treatment response and the above markers in patients receiving n-CRT for LARC.

Material and Methos: The pathology results of 113 patients who underwent TME after n-CRT were divided into 4 groups according to the modified ryan tumor regression grade (TRG) classification. Among these groups, NLR, PLR and CEA levels, which are considered prognostic markers in response evaluation, were compared with their changes before and after neoadjuvant treatment.

Results: While 11 (9,7%) patients had pCR (TRG 0), 41 (36,3%) patients had good response (TRG 0 and 1), 72 (63,7%) patients had a poor response (TRG 2 and 3) to n-CRT. While the initial prognostic markers were similar between the groups, post-n-CRT values were found to be significantly lower in the group with good response.

Discussion: It is not possible to predict n-CRT response in LARC patients at the time of diagnosis, but NLR, PLR or CEA values and changes in these values may be useful in predicting treatment response.

**Keywords**

Rectal cancer; Neutrophil-to-lymphocyte ratio (NLR); Platelet-to-lymphocyte ratio (PLR); Carcinoembryonic antigen (CEA)

DOI: 10.4328/ACAM.20431 Received: 2020-12-06 Accepted: 2020-12-21 Published Online: 2020-12-27 Printed: 2021-01-01 Ann Clin Anal Med 2021;12(1):49-53
Corresponding Author: Hüseyin Çiyiltepe, Fatih Sultan Mehmet Training and Research Hospital, Department of Gastroenterological Surgery Istanbul, Turkey.
E-mail: drciyiltepe@hotmail.com P: +90 5075830408
Corresponding Author ORCID ID: https://orcid.org/0000-0003-3048-1784

## Introduction

The standard treatment for locally advanced (T3-4 and/or N +) middle and distally located rectal cancer is Total Mesorectal Excision (TME) and adjuvant chemotherapy, as defined by Heald et al. in 1982 after neoadjuvant chemo-radiotherapy (n-CRT) [1,2]. This method reduces local recurrence rates and has positive effects on survival, but it also has life-threatening morbidities such as an anastomotic leak, pelvic sepsis or, has adverse effects on long-term quality of life, such as sexual and bladder dysfunctions [2]. In 10-30% of patients who undergo TME after n-CRT, no tumor cells are seen in the pathology specimen, and it is considered as pathological complete response (pCR) (ypT0N0M0, Stage 0 disease) [3]. In 2004, Habr-Gama et al. published the 10-year follow-up results of 71 distal rectal cancer patients who developed a clinical complete response after n-CRT and reported no difference in overall survival and disease-free survival between the follow-up group and the surgical group. In addition, there was a higher rate of morbidity and stoma formation in the surgical arm. Thus, the foundations of Watch and Wait (W&W) or Nonoperative Management (NOM) were laid in the treatment of rectal cancer [4]. The nonoperative management of these patients is still controversial among investigators, especially concerning the definition of clinical complete response (cCR). In all studies, very strict clinical (Digital rectal examination (DRE)), endoscopic (rigid proctoscopy), laboratory (carcinoembryonic antigen (CEA) level) and radiological criteria (Magnetic resonance (MR) or endorectal ultrasound (ERUS)) to define n-CRT response as cCR are applied [5]. According to this, the absence of residual tumor, ulcer, or stenosis in DRE, the presence of telangiectasis with the whitening of the mucosa in proctoscopy, and the presence of fibrotic changes in the rectum and the absence of metastatic lymph nodes in the mesorectum in the evaluation with MR or ERUS are defined as cCR. However, all of these findings are dependent on the person making the assessment [4].

The Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been shown to be prognostic factors for many solid tumors, and an increase in these ratios indicates a poor prognosis [6,7]. Besides, high CEA values at the time of diagnosis of rectal cancers indicate a poor prognosis, while normalization of this value after n-CRT [8] increases the rate of cCR. This study aimed to compare the response rate [9] in pathology evaluation of patients who underwent n-CRT and TME due to locally advanced rectal tumor, and NLR, PLR, and CEA values at the time of diagnosis and after neoadjuvant therapy, and try to determine the effect of changes in these values on the complete response.

## Material and Methods

This study was conducted between January 2015 and December 2018 at the Gastroenterology Surgery Clinic of Kartal Kosuyolu High Specialty Training and Research Hospital involving 113 patients who were diagnosed with local advanced rectal cancer (LARC) and underwent TME after neoadjuvant chemo-radiotherapy (Capecitabine + long-course chemo/RT (45–50 Gy in 25–28 fractions to the pelvis) or infusional 5-FU + long-course RT).All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and this study was approved by the local ethics committee.

Demographic data of the patients such as age, gender, the distance of the tumor from the dentate line, the time between neoadjuvant therapy and the operation (restaging time), and the type of surgery performed ((Low anterior resection (LAR) vs Abdominoperineal resection (APR), laparoscopic vs open) were recorded retrospectively from the patient files.

CEA, NLR, and PLR were recorded before and after the neoadjuvant therapy of these patients. While pre-treatment values were accepted as values at which rectal cancer was diagnosed, post-neoadjuvant values were taken as values in restaging performed after the end of treatment.

In the pathological evaluation of the specimen removed, the tumor type, presence of lymphovascular (LVI) and perineural (PNI) invasion, the presence of metastatic lymph node, and tumor regression grades were examined. In the pathological examination, neoadjuvant treatment response was made according to the modified Ryan tumor regression classification [9]. According to this, 0 (complete response) means no viable cancer cell, 1 (near-complete response): single cells or rare small groups of cancer cells, 2 (partial response): residual cancer with evident tumor regression, but more than single cells rare small groups of cancer cells, 3 (poor or no response): extensive residual cancer with no evident tumor regression.

The patients were divided into two groups according to the regression grade of the tumor; TRG 0 and 1 are 'good responders', 2 and 3 are 'poor responders'. The relationship between changes in CEA, NLR, PLR values before/after neoadjuvant treatment and the TRG groups were compared.

***Statistical analysis:***

A statistical software package (SPSS 21 Inc., Chicago, IL, USA) was used for biostatistical analysis. The data obtained from the patients participating in the study were expressed as mean, standard deviation values, and in percentages where appropriate. Comparison of parametric data between 4 independent groups was made using the One-way Anova test. Homogeneity test of variances (Levene's test) was considered parametric, and the Bonferroni test was applied in the postHoc analysis. Nonparametric tests were performed using the Kruskal-Wallis H test. If a difference was found between the groups, a new p-value was obtained by the Bonferroni correction. The Mann-Whitney U test was applied to the parameters found to be significant according to the new p-value. Using receiving operating characteristic (ROC) curves, cutoff values for CEA, NLR, and PLR values at baseline and after n-CRT were determined. Categorical groups were compared by the Chi-Square test.

## Results

Between January 2015 and December 2018, a total of 113 LARC patients were operated on after n-CRT. Sixty-seven (59.3%) patients were male, 46 (40.7%) were female, and the median age was 59.4 (SD ± 11.2) years. Low anterior resection was performed in 91 (80.5%) patients, and abdominoperineal resection was performed in 22 (19.5%) patients. The average distance from the dentate line of the tumor was 5.49 cm (2.09 cm in those with APR, 6.31 cm in those with LAR, $p < 0.05$).

**Table 1.** Demographic data of patients and general pathological features of tumor specimen

| Number of Patients | 113 |
|---|---|
| Age | 59,4 (SD:11,2) |
| Gender (n, %) | |
| Female | 46 (40,7) |
| Male | 67 (59,3) |
| Distance from dentateline (cm) | 5,49 (Range:0-9 cm) (LAR: 6,31 cm, APR:2,09 cm, p=0,00)[a] |
| Re-evaluating time (weeks) | 6,91 (Range:6-9 weeks) |
| Operation (n,%) | |
| LAR | 91 (80,5) |
| APR | 22 (19,5) |
| OperationType (n, %) | |
| Laparoscopic | 40 (35,4) |
| Open | 73 (64,6) |
| Modified Ryan TRG (n,%) | |
| 0 | 11 (9,7) |
| 1 | 30 (26,5) |
| 2 | 38 (33,6) |
| 3 | 34 (30,1) |
| LVI (n, %) | |
| Undetermined | 11 (9,7) |
| Positive | 10 (8,8) |
| Negative | 92 (81,4) |
| PNI (n, %) | |
| Undetermined | 11 (9,7) |
| Positive | 18 (15,9) |
| Negative | 84 (74,3) |
| Metastatic Lymph Node | |
| Positive | 40 (35,4) |
| Negative | 73 (64,6) |

LAR: Low Anterior Resection, APR: Abdominal Perineal Resection, TRG: Tumor Regression Grade, LVI: Lymphovascular invasion, PNI: perineural invasion, [a]Oneway Anova

The median time to restaging the tumor after neoadjuvant therapy was 6.91 weeks and no difference was observed between the groups. Open surgery was performed in 73 (64.6%) patients, while the laparoscopic technique was used in 40 (35.4%) patients. Demographic data of the patients are given in Table 1.

According to the modified Ryan tumor regression classification of the extracted specimen, 11 (9.7%) patients were complete (TRG 0), 30 (26.6%) patients moderate (TRG 1), 38 (33.6%) patients minimal (TRG) 2) and 34 (30.1%) patients were evaluated as poor n-CRT response (TRG 3).

When the specimens were evaluated in terms of LVI, 81.4% of them were negative, 8.8% were positive, while 9.7% of the specimens could not be evaluated due to complete response. Similarly, when the PNI was evaluated, 74.3% were negative, 15.9% were positive, and 9.7% could not be evaluated. While no metastatic lymph node was found in 73 (64.6%) patients, 40 (35.4%) patients had lymph node metastasis. The general pathological features of tumor specimens are given in Table 1.

According to the modified Ryan classification, the patients in the 4 groups were similar in terms of age and restaging time. Female patients made up the majority in the TRG2 group (% 68.4, p:0,00). The n-CRT response was worse in tumors located far from the dentate line (According to TRG classification, the distance of the tumor from the dentate line is 4.18 cm, 4.46 cm, 5.81 cm, 6.47 cm, p: 0.00, respectively).

CEA, NLR, PLR values during initial and after n-CRT restaging are given in Table 2. While there was no statistical difference between the groups in the initial values, the values after the n-CRT were statistically different between the groups.

Differences between initial values and post-n-CRT values were also evaluated in Table 2.

While the decrease in CEA value was found to be a good prognostic for TRG, the increase in CEA, NLR, and PLR worsened the n-CRT response and increased the TRG.

**Table 2.** Relationship between change of prognostic markers and TRG

| Changes in prognostic parameters | TRG 0 (n:11) | TRG 1 (n:30) | TRG 2 (n:38) | TRG 3 (n:34) | P value | Good response (n:41) | Poor response (n:72) | P value |
|---|---|---|---|---|---|---|---|---|
| CEA Initial | 2,84 | 6,52 | 4,33 | 3,76 | 0,14[a] | 5,54 | 4,06 | 0,18[a] |
| CEA aftern-CRT | 2,09 | 3,21 | 4,57 | 5,68 | 0,01[a1] | 2,91 | 5,09 | 0,00[a] |
| Std. Deviation | 1,09 | 6,51 | 1,66 | 2,16 | | 5,69 | 2,07 | |
| p-value[c] | 0,04 | 0,00 | 0,37 | 0,00 | | 0,00 | 0,00 | |
| NLR Initial | 3,80 | 4,37 | 4,12 | 5,03 | 0,44[b] | 4,22 | 4,55 | 0,53[a] |
| NLR after n-CRT | 2,75 | 3,93 | 5,52 | 6,33 | 0,00[b1] | 3,61 | 5,90 | 0,00[b] |
| Std. Deviation | 2,74 | 1,74 | 4,10 | 4,05 | | 2,03 | 4,05 | |
| p-value[c] | 0,23 | 0,17 | 0,04 | 0,07 | | 0,06 | 0,00 | |
| PLR Initial | 189,2 | 215,7 | 236,3 | 244,1 | 0,43[b] | 208,6 | 239,9 | 0,13[b] |
| PLR after n-CRT | 146,3 | 207,3 | 333,3 | 428,6 | 0,00[a2] | 190,9 | 378,3 | 0,00[a] |
| Std. Deviation | 92,08 | 106,6 | 157,7 | 269,6 | | 102,9 | 216,3 | |
| p-value[c] | 0,15 | 0,67 | 0,00 | 0,03 | | 0,27 | 0,00 | |

CEA: Carcinoembryonicantigen, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, n-CRT: Neoadjuvant Chemoradiotherapy
[a] Kruskal-Wallis H test, [a1] Mann-Whitney U Test (TRG3 vs TRG0 and TRG1, p-values <0,0125), [a2] Mann-Whitney U Test (TRG3 vs all other groups, TRG2 vs TRG0 and TRG1, p-values <0,0125)
[b] Oneway Anova, [b1] postHoc Bonferroni (TRG3 vs TRG0 and TRG1, p-values <0,0125), [c] Paired Samples T-Test

**Table 3.** Distribution of CEA, NLR and PLR cutoff values by good or poor response groups

| | N | Good response N (%) | Poor Response N (%) |
|---|---|---|---|
| Initial CEA | | | |
| <3,45 | 72 | 27 (37,5) | 45 (62,5) |
| ≥3,45 | 41 | 14 (34,1) | 27 (65,9) |
| CEA after n- CRT | | | |
| <2,8 | 45 | 27 (60,0) | 18(40,0) |
| ≥2,8 | 68 | 14 (20,6) | 54 (79,4) |
| Initial NLR | | | |
| <6,8 | 98 | 40 (40,8) | 58 (59,2) |
| ≥6,8 | 15 | 1 (6,7) | 14 (94,3) |
| NLR after n- CRT | | | |
| <5,04 | 70 | 37 (52,9) | 33 (47,1) |
| ≥5,04 | 43 | 4 (9,3) | 39 (90,7) |
| Initial PLR | | | |
| <163,3 | 40 | 20 (50,0) | 20 (50,0) |
| ≥163,3 | 73 | 21 (28,8) | 52 (71,2) |
| PLR after n- CRT | | | |
| <255,2 | 47 | 37 (78,7) | 10 (21,3) |
| ≥ 255,2 | 66 | 4 (6,1) | 62 (93,9) |

When patients with TRG 0 and 1 were grouped as 'good responders' and those with TRG 2 and 3 as 'poor responders', the initial CEA, NLR, and PLR values were similar, but the CEA, NLR, PLR values after n-CRT differed between the groups (Table 2). In the same table, the changes in these prognostic factors were compared between the two groups. Accordingly, while these values increased in the 'poor responder' group, it was found that CEA decreased in the other group.

ROC analysis was performed for the initial and post-n-CRT values of CEA, NLR, and PLR, and the cut-off values were determined. Accordingly, the initial CEA, NLR, PLR were 3.45, 6.8, 163.3, respectively, while the same values after n-CRT were 2.8, 5.04, 255.2. Taking these values, the evaluation of the tumor's response to n-CRT is given in Table 3.

## Discussion

NLR / PLR values, defined as prognostic factors for many solid tumors, and CEA level as a colorectal tumor marker, are easily measurable and cost-effective tests. In this study, pathology results of 113 LARC cases who underwent TME after n-CRT were examined, and significant correlations were found between the prognostic markers mentioned above and n-CRT response. While 11 (9.7%) patients had pCR (TRG 0), 41 (36.3%) patients had good response (TRG 0 and 1) and 72 (63.7%) patients had poor response to n-CRT (TRG 2 and 3). The CEA, NLR, and PLR values of these patients at the time of diagnosis were similar. However, while all of these values decreased in the group with a good response after n-CRT, the increase in these values was noted in patients with poor response.

The relationship between cancer and inflammation has been studied for years, and it is known that the systemic inflammatory response causes angiogenesis, apoptosis inhibition, and DNA damage [10]. NLR and PLR are systemic inflammation markers. While increased neutrophil and platelet counts facilitate tumor growth, invasion, and metastasis through secreted neuromediators, the decrease in lymphocyte count worsens the prognosis through weakened anti-tumor immunity [11]. Many studies in the literature have reported that a high NLR or PLR is associated with a poor survival outcome in solid tumors (esophagus, lung, or stomach) [12,13].

On the other hand, while CEA determines the prognosis of colorectal cancer in the preoperative period, it is a diagnostic tool for early diagnosis of resectable and non-resectable relapses, which have an important impact on survival and quality of life in the postoperative period [14].

The main purpose of n-CRT in the treatment of LARC is to achieve tumor downstaging/pathological complete response (pCR) and prevent local recurrence. In the literature, data on pCR after n-CRT vary from 6 to 34% [15]. In our study, the rate of pathological complete response was 9,7%, which was lower than in many studies in the literature. While the mean restaging time in this study was 6.9 weeks, there are many studies in the literature showing that the pathological complete response rates obtained with prolongation of this period increased [15-17]. In contrast, the French GRECCA-6 study, which compared the 7 and 11 weeks waiting time, showed that there was no difference in pCR rates between the groups (15.0% vs 17.4%), but the 11 weeks group showed higher postoperative complications (32% vs 44.5%) and the quality of TME samples (90% vs 78.7%) was poorer [18].

Predicting which patient will develop pCR is important both for the prognosis of this patient group and for making a diagnosis of cCR in the nonoperative treatment of rectal tumor.

Carruthers et al. were the first to suggest that NLR before CRT is a predictive factor for prognosis in rectal cancer patients receiving n-CRT, and showed that patients with NLR≥5 before CRT had worse OS and DFS [19].

In the study on 87 LARC patients, Caputo et al. found the NLR and d-NLR cut-off points as 2.8 and 3.8, respectively, and reported that patients with values above these cut-off points had a worse tumor regression grade response and worse clinical outcome [20].

Sung et al. reported that pre and post-n-CRT NLR values were prognostic factors in their study conducted on 110 patients with T3/4 or lymph node-positive rectal cancer, and that the risk of distant metastasis increased with high post-n-CRT NLR [11]. In this study, the pre-treatment NLR cut off point was accepted as 1.75 and after treatment as 5.14. Pathological complete response was found to be higher in patients below these values, but it was not statistically significant.

On the contrary, Shen et al. found 18.8% pCR in their study of 202 LARC patients, and the pre-treatment NLR value less or higher than 3 was not different in terms of T downstaging and pCR (65.8% vs 34.2%, respectively; p = 0,067), also reported no effect on OS and DFS [21]. Lee et al. also reported that NLR would not be a suitable prognostic factor for predicting pCR, but pre-treatment PLR value and PLR value during treatment are parameters that can be used to evaluate n-CRT response. In the study where 15.9% of 297 patients had pCR, they reported that the pre-treatment PLR was 121.9 and 266.6 at the third week of treatment, and this change had prognostic significance in multivariate analyzes [22].

Another marker that determines the prognosis of the tumor is CEA. In the study by Wallin et al. who had pCR in 96 (20.4%) of 469 patients, a pre-treatment CEA value of <5ng/ml was found to be associated with the complete tumor regression rate [23]. Perez et al. in their studies evaluated 170 LARC patients and reported that CEA values before and after n-CRT were 9.3 and 4.4, respectively, and that the decrease in CEA level after treatment was significant for both pCR and cCR [24].

In another series of 141 patients with similar pre-treatment CEA values, it was reported that CEA after n-CRT was found to be lower in the pCR group (1.7 vs 2.4; p = 0.001), and low CEA after n-CRT was an independent predictive factor ( OR = 1.74). Besides, the normalization of CEA is a more highly significant predictor of pCR (OR = 64,8) [8].

In our study, although we could not find a relationship between prognostic markers at the time of diagnosis and tumor response in patients with LARC, we found that values after n-CRT could be used as prognostic indicators to predict tumor response. Also, we found that the changes between the values at the time of diagnosis and the values after n-CRT also affected tumor regression grade.

The limitation of this study is that it is retrospective and the number of patients is low. Besides, the lack of a more detailed grouping according to clinical stages at the time of diagnosis is also an important factor limiting the study.

In conclusion, it is not possible to predict the n-CRT response at the time of diagnosis in LARC patients, but NLR, PLR, or CEA values and changes in these values may be useful in predicting treatment response.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

***Funding:*** *None*

***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

***References***

*1. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? Br J Surg. 1982;69(10):613–6.*

*2. Sauer R, Beacker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.*

*3. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty BD, Guillem JG, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg. 2002;194(2):131–5.*

*4. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Sousa AHS, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711–7.*

*5. Habr-Gama A, São Julião GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: the impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg. 2019, 269(1):102-7.*

*6. Shen L, Zhang H, Liang L, Li G, Fan M, Wu Y, et al. Baseline neutrophil-lymphocyte ratio (≥ 2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Radiation Oncology. 2014;9(1):295.*

*7. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, et al. Prognostic value of PLR in various cancers: a meta-analysis. PloS One. 2014;9(6):e101119. DOI: 10.1371/journal.pone.0101119.*

*8. Kleiman A, Al-Khamis A, Farsi A, Kezouh A, Vuong T, Gordon PH, et al. Normalization of CEA levels post-neoadjuvant therapy is a strong predictor of pathologic complete response in rectal cancer. J Gastrointest Surg. 2015;19(6):1106-12.*

*9. Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology. 2005;47(2):141-6.*

*10. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436–44.*

*11. Sung S, Son SH, Park EY, Kay CS. Prognosis of locally advanced rectal cancer can be predicted more accurately using pre- and post- chemoradiotherapy neutrophil-lymphocyte ratios in patients who received preoperative chemoradiotherapy. PLoS One. 2017;12(3):e0173955.*

*12. Hyder J, Boggs DH, Hanna A, Suntharalingam M, Chuong MD. Changes in neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios during chemoradiation predict for survival and pathologic complete response in trimodality esophageal cancer patients. J Gastrointest Oncol. 2016;7(2):189.*

*13. Unal D, Eroglu C, Kurtul N, Oguz A, Tasdemir A. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis. Asian Pac J Cancer Prev. 2013;14(9):5237-42.*

*14. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, MacDonald JS, et al. ASCO 2006 update ofrecommendations for the use of tumor markers in gastrointestinalcancer. J Clin Oncol. 2006;24(33):5313-27*

*15. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer. Ann Surg. 2016;263(3):454-64.*

*16. Macchia G, Gambacorta MA, Masciocchi C, Chiloiro G, Mantello G, Benedetto Md, et al. Time to surgery and pathologic complete response after neoadjuvantchemoradiation in rectal cancer: A population study on 2094 patients. Clin Transl Radiat Oncol. 2017;4:8-14.*

*17. Evans J, Bhoday J, Sizer B, Tekkis P, Swift R, Perez R, et al. Results of a prospective randomised control 6 vs 12 trial: is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? Ann Oncol. 2016;27(Suppl. 6):4520.*

*18. Lefevre HJ, Mineur L, Kotti S, Rullier E, Rouanet P, Chaisemartin Cd, et al. Effect of Interval (7 or 11 weeks) Between NeoadjuvantRadiochemotherapy and Surgery on Complete PathologicResponse in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). J Clin Oncol. 2016;34(31):3773-80.*

*19. Carruthers R, Tho LM, Brown J, Kakumanu S, McCartneyE, McDonald AC. Systemic inflammatory response isa predictor of outcome in patients undergoing preoperativechemoradiation for locally advanced rectal cancer. Colorectal Dis. 2012;14(10):e701–7.*

*20. Caputo D, Caricato M, Coppola A, La Vaccara V, Fiore M, Coppola R. Neutrophil to lymphocyte ratio (NLR) and derived neutrophil to lymphocyte ratio (d-NLR) predict non-responders and postoperative complications in patients undergoing radical surgery after neo-adjuvant radio-chemotherapy for rectal adenocarcinoma. Cancer Invest. 2016;34(9):440-51.*

*21. Shen J, Zhu Y, Wu W, Zhang L, Ju H, Fan Y, et al. Prognostic role of neutrophil-to-lymphocyte ratio in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Med Sci Monit. 2017;23:315-24.*

*22. Lee JH, Song C, Kang SB, Lee HS, Lee KW, Kim JS. Predicting pathological complete regression with haematological markers during neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Anticancer research. 2018; 38(12):6905-10.*

*23. Wallin U, Rothenberger D, Lowry A, Luepker R, Mellgren A. CEA–a predictor for pathologic complete response after neoadjuvant therapy for rectal cancer. Dis Colon Rectum. 2013;56(7):859-68.*

*24. Perez RO, São Julião GP, Habr-Gama A, Kiss D, Proscurshim I, Campos FG, et al. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemoradiotherapy for distal rectal cancer. Dis Colon Rectum. 2009;52(6):1137-43.*

***How to cite this article:***

*Hüseyin Çiyiltepe, Ebubekir Gündeş, Durmuş Ali Çetin, Ulaş Aday, Emre Bozdağ, Selçuk Gülmez, Orhan Uzun, Aziz Serkan Senger, Erdal Polat, Mustafa Duman. Can NLR/PLR/CEA be a marker for predicting a complete pathological response in locally advanced rectal cancer? Ann Clin Anal Med 2021;12(1):49-53*